REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16-24 and 40-64 the only claims pending in this application.

RESTRICTION REQUIREMENT

The Office Action has set forth a restriction requirement between Group I (Claims 16-24), Group II (Claims 40-48), Group III (Claims 49-55), Group IV (Claims 56-64), and has constructively imposed election of the claims of Group I (Claims 16-24).

The Applicants respectfully disagree with the restriction requirement and hereby request that all the claims be prosecuted together. As stated in the MPEP §803, if search and examination of an entire application can be made without serious burden, the examiner must examine the entire application on the merits.

Applicants respectfully submit that it would not be unduly burdensome to examine all of the claims of Groups I, II, III, and IV together. These claims are directed to methods of inhibiting a binding event between a target protein and a binding protein, where the methods differ with respect to the features of the target protein ligand and the blocking protein ligand. In particular, Group I (Claims 16-24), which group the Office Action has constructively elected, are directed to a method using a bifunctional molecule, wherein the target protein ligand specifically binds to a target protein and the blocking protein ligand specifically binds to a blocking protein.

The difference between the claims of Group II (Claims 40-48) and the claims of Group I, is that the binding affinity of the target protein ligand to the target protein is about 10^{-4} M and the affinity of the blocking protein ligand to the blocking protein is about 10^{-4} M. The difference between the claims of Group III (Claims 49-55) and the claims of Group I and Group II, is that the binding affinity of the target protein ligand to the target protein is about 10^{-4} M and the blocking protein ligand is further defined as a peptidyl-prolyl isomerase. The difference between the claims of Group IIV (Claims 56-64) and the claims of Group I-III, is that the target protein ligand and blocking protein ligand are further defined as being known to specifically bind to the target protein or blocking protein.

It is the Applicants' position that it would not be unduly burdensome to examine all of the

claims together in the present application. In particular, the Applicants assert that the search to identify art relevant to the claims of Group I has already identified the art relevant to the claims of Groups II, III, and IV. As noted above, the claims of Groups II-IV further define the features of the target protein ligand and the blocking protein ligand of the claims of Group I.

Moreover, the Applicants stress that, as noted in the Office Action, all four groups are classified in the same class and subclass, i.e., class 436, subclass 518. Accordingly, the Applicants request that the claims of Groups I-IV be examined together.

Rejection Under 35 U.S.C. § 112, First Paragraph – Enablement

The rejection of Claims 16-24 has been maintained under 35 U.S.C. § 112, first paragraph, for allegedly not describing the subject matter in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

In particular, the Office Action maintains that, although the specification is enabling for the production and *in vitro* utility of non-naturally occurring bifunctional inhibitor molecules, the specification does not reasonably provide enablement for inhibiting protein-protein interaction *in vivo* with the non-naturally occurring bifunctional molecules.

As recited in the Amendment filed on February 3, 2005, the Applicants maintain that the specification provides ample disclosure to enable one skilled in the art to practice the claimed invention.

In support of the Applicants position that the specification provides enablement for the full scope of the claims, the Applicants cited Gestwicki et al., Science 306:865-869 (2004) (Exhibit A), a research article published after the filing date of the present application that reported successful use of the bifunctional inhibitor molecule to inhibit target and binding protein interaction *in a cell*. The Office Action, however, asserts that the argument is not persuasive because "Gestwicki et al. does not teach in vivo application of the bifunctional molecule" (Office Action, page 12).

The Applicants respectfully disagree. The Applicants stress that Gestwicki et al., **establishes that inhibition of such protein-protein interactions can be achieved *in vivo in a cell***. In particular, Gestwicki et al., discloses use of the bifunctional inhibitor molecule in preventing interaction and aggregation of β-amyloid (Aβ) peptides generated by proteolytic

cleavage of amyloid precursor protein *in a cell.* The authors disclose use of a bifunctional inhibitor molecule comprising a binding molecule that binds FK506 binding protein and a targeting molecule that interacts with aggregating Aβ. The authors, **using the experiments described in the present application**, show that application of the bifunctional inhibitor molecules to cultured hippocampal neurons results in distinct changes in cellular morphology as well as aggregation and distribution of amyloid fibrils (see page 866, column 3 through page 4 and Figs. 2 and 4). There is no reason to believe that such inhibition of protein-protein interaction in a cultured cell would be any different than inhibition of protein-protein interaction in a cell in a host.

Therefore, as demonstrated by the Gestwicki et al. group (Exhibit A), the guidance provided by the Applicants was entirely sufficient to inhibit protein-protein interactions *in vivo in a cell* using a bifunctional molecule. Based on such evidence it is clear that once the bi-functional molecule enters a cell, it is capable of inhibiting the binding event between the target protein and the binding protein.

Moreover, the claims of the application do not require a therapeutic result be achieved upon administration of the bi-functional molecules. Rather, the claims only require that a binding event between a target protein and a binding protein be inhibited. Therefore, the concerns that are cited in the Office Action, with respect to treatment and disease condition are not relevant to claims directed to inhibition of a binding event between a target protein and a binding protein. As noted in the response filed on February 3, 2005, the specification provides ample disclosure with respect to use of the bifunctional molecules for inhibiting a binding event. In addition, as noted above, Gestwicki et al. shows that, by using the techniques in this application, successful inhibition of binding interactions between a target protein and a binding protein can be achieved and in a predictable manner *in vivo in a cell.*

In view of such guidance provided in the specification, in combination with the knowledge of one of skill in the art, any experimentation that may be necessary is reasonable. Moreover, as exemplified by Gestwicki et al., such inhibition of protein-protein interaction can be achieved *in vivo in a cell.* Therefore, the results described in Gestwicki et al., support the Applicants' position that the quantity of experimentation necessary to practice the invention is not as high as asserted by the Office Action. As such, the Applicants respectfully submit that the

specification, coupled with the information available in the relevant art, does enable one of skill in the art to practice the claimed invention without undue and excessive experimentation.

In sum, the Applicants maintain that the amount of experimentation required to practice the subject invention would not be undue and excessive because working examples have been provided, guidance is given on how to generate such compounds, and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the remarks presented herein and in view of the relevant *Wands* factors, as applied in the response filed on February 3, 2005.

The claims pending in the present application are fully enabled by the specification, in view of the description and examples provided therein as well as exemplified by the work reported by Gestwicki et al., as found in Exhibit A to this response. The Applicants have discovered and are claiming a new approach to inhibiting protein-protein interactions, and have enabled this approach with extensive description of the nature of the compounds used and specific representative exemplification. **As demonstrated by the Gestwicki et al. group (Exhibit A), the guidance provided by the Applicants was entirely sufficient to produce a bifunctional molecule that is capable of inhibiting protein-protein interaction between a target protein and binding proteins *in vivo in a cell.*** Therefore, there is no reason to think that such a disclosure cannot be extrapolated to the pending claims.

For at least the reasons provided above, the claims are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-166.

Respectfully submitted,
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Date: August 18, 2005 By: _____
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